Essential Hypertension—Where Are We Going?

Discussant
HARLAN E. IVES, MD, PhD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

(Ives HE: Essential hypertension—Where are we going? West J Med 1990 Oct; 153:415-420)

FLOYD C. RECTOR, MD*: *Great advances have been made in the treatment of hypertension, and long-term therapy has proved effective in reducing the risk of cardiovascular disease. The costs and complications of current therapy are often troublesome, and the development of more effective treatment ultimately requires defining the mechanisms underlying the disease. For common, "essential" hypertension, these mechanisms are unknown, but several attractive and instructive theories have been proposed. Harlan Ives, MD, Chief of the Division of Nephrology, has been active in studies of these theories and reviews their promise and problems in efforts to better understand and more effectively treat the disease.*

HARLAN E. IVES, MD, PhD†: Despite intensive research over many years, the pathogenesis of essential hypertension remains mysterious. Patients with essential hypertension do not have the high circulating levels of renin that characterize renal artery stenosis, nor do they have the volume overload and suppressed renin-angiotensin system that characterizes primary hyperaldosteronism. At an intravascular volume that is close to normal, patients with essential hypertension maintain an elevated vasomotor tone, or an elevated vasomotor tone develops with increased salt intake. A mechanism is needed to explain this increased vasomotor tone.

One of the major hypotheses for the pathogenesis of essential hypertension focuses on the ion transport systems that regulate salt excretion by the kidney and that also control the intracellular ionic milieu of all cells. It is proposed that factors that regulate salt transport by renal epithelial cells may also affect the intracellular ionic milieu in vascular smooth muscle cells. By altering the intracellular sodium (Na^+), calcium (Ca^{2+}), hydrogen (H^+), or other ions, these transport systems have the potential to regulate vascular smooth muscle contractile activity. Defects in the activity or regulation of one or more of these transport systems have been proposed to cause certain forms of hypertension. In this review I will critically assess the basis for this contention and propose several areas for future investigation into the pathogenesis of essential hypertension.

*Professor and Chair, Department of Medicine, University of California, San Francisco (UCSF), School of Medicine.

†Chief, Division of Nephrology, Cardiovascular Research Institute, UCSF.

Ion Transport Defects and Hypertension

Most of the recent thinking on the role of ion transport defects in hypertension flows from the hypothesis, first broached by Haddy and Overbeck[1] and by Blaustein,[2] that essential hypertension is caused by the production of circulating Na^+ transport inhibitors acting on renal epithelial cells and vascular smooth muscle cells. This hypothesis drew much of its force from earlier observations by Dahl and co-workers that salt-sensitive hypertension in rats could be transferred by renal transplantation or by the exchange of fluids in parabiotic experiments.[3] This led to the idea that, in response to salt loading, the kidney produces a circulating substance that causes both natriuresis and vasoconstriction. Work carried out over a number of years by Overbeck, Pamnani, Clough, and Haddy (reviewed by Haddy and Overbeck[1]) suggested that this circulating substance might be an inhibitor of the Na^+-potassium ion (K^+) adenosine triphosphatase (ATPase), or Na^+, pump. Such an inhibitor would cause natriuresis by reducing Na^+ reabsorption by renal epithelial cells.

Sodium pump inhibitors would also be expected to affect vascular smooth muscle function. In these cells, the inhibitors would cause the cell Na^+ content and volume to rise and the membrane potential to fall. Blaustein argued that increased intracellular Na^+, acting on a plasma membrane Na^+-Ca^{2+} exchange system, would then lead to increased intracellular Ca^{2+} (Figure 1).[2] Increased vascular smooth muscle cell Ca^{2+}, by its well-known action on the contractile machinery, would in turn lead to the contraction of vascular smooth muscle cells or increased responsiveness to vasoconstrictors. Increased vascular tone would raise the blood pressure, contributing to the desired natriuresis. In normotensive persons, a steady state would be achieved wherein Na^+ intake would be matched by Na^+ excretion at a plasma volume and blood pressure close to normal. A "salt-sensitive" hypertensive person, by failing to excrete the Na^+ load at an adequate rate, would remain volume overloaded, would continuously produce the natriuretic or hypertensive substance, and would become chronically hypertensive as long as salt intake remained unchanged.

This hypothesis, while seductive in its simplicity and broad explanatory power, has never been adequately sub-

This work is supported in part by grants (DK-34127 and HL-41210) from the National Institutes of Health and from the National Dairy Board (administered in cooperation with the National Dairy Council). Dr Ives is an Established Investigator of the American Heart Association.

Reprint requests to Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
UCSF = University of California, San Francisco

stantiated. Numerous studies by various investigators have examined the Na^+-K^+ ATPase activity, as well as a number of putative circulating inhibitors (digitalis-"like" factors) in normotensive and hypertensive persons. Space prohibits a thorough review of this information, which has been extensively reviewed elsewhere. Studies of both human and experimental hypertension, however, have failed to show a consistent correlation between Na^+-K^+ ATPase activity and blood pressure. While circulating inhibitors of the Na^+ pump have been found,[4] their precise chemical makeup is not clear, the stimulus to their production is unknown, and, most important, it is not known whether they actually cause hypertension. In a recent provocative editorial, Kelly and Smith even question the assumption that the digitalis binding site on the Na^+-K^+ ATPase is the receptor for a circulating factor.[5] They raise the possibility that this site may play a role in intracellular trafficking of the enzyme. The only convincing natriuretic substance found thus far, atrial natriuretic factor, is not a potent inhibitor of Na^+-K^+ ATPase, and, contrary to the hypothesis outlined above, it is not a vasoconstrictor but a vasodilator.

Variants of the Haddy-Blaustein hypothesis argue that abnormal cell Na^+ in vascular smooth muscle cells might not arise from decreased Na^+ efflux through Na^+-K^+ ATPase but, rather, from increased Na^+ uptake through Na^+-entry pathways. A similar defect on the apical membrane of renal epithelial cells would enhance renal sodium reabsorption and thus reduce urinary Na^+ excretion. Such increased Na^+ entry into renal epithelial cells would not be expected as a response to volume overload but, rather, may play a role in the development of volume overload. Sodium entry pathways that could participate in enhanced Na^+ uptake include the Na^+-H^+ exchanger, the Na^+, K^+, chloride (Cl^-) transporter, and the Na^+ channel. Of these, the system that has received the most recent attention is the Na^+-H^+ exchanger.

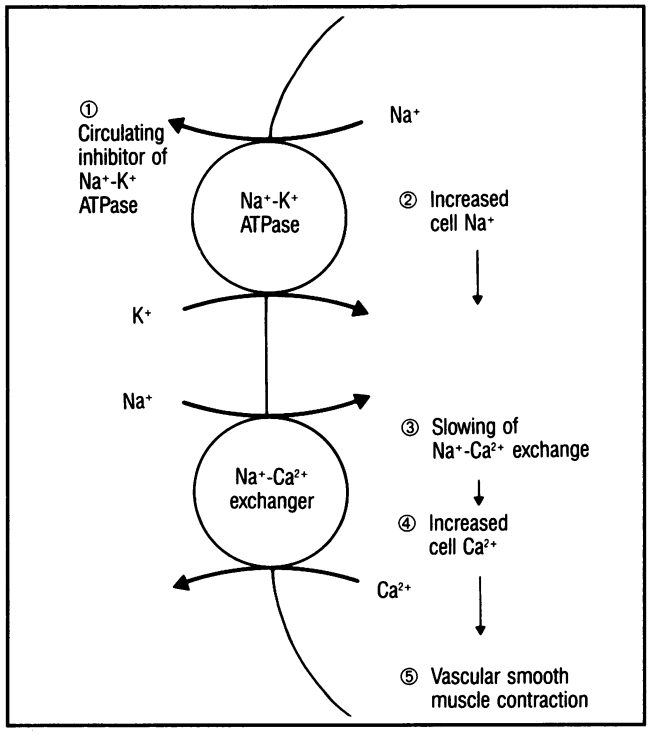

Figure 1.—The Blaustein hypothesis proposes that circulating sodium ion (Na^+) transport inhibitors elaborated during volume overload might lead to a contraction of vascular smooth muscle cells by an elevation in the intracellular calcium ion (Ca^{2+}) concentration. ATPase = adenosine triphosphatase

Sodium-Lithium and Sodium-Hydrogen Exchange

The possibility that Na^+-H^+ exchange might be involved in the development of hypertension was first brought forward after the discovery ten years ago that erythrocytes from hypertensive patients have increased erythrocyte Na^+-lithium (Li^+) exchange activity when compared with normotensive persons.[6] While it is still not clear what role the Na^+-Li^+ countertransport plays in cellular physiology, it seems plausible that this system represents a mode of operation of the ubiquitous Na^+-H^+ exchanger. Among its many functions, the Na^+-H^+ exchanger is the most important Na^+ uptake pathway on the apical membrane of the proximal tubule epithelial cell and therefore plays an essential role in Na^+ transport by this nephron segment (Figure 2). It is still not known whether red cell Na^+-Li^+ exchange and proximal tubule Na^+-H^+ exchange represent the same transport system, but it is known that Li^+ is an excellent substrate for the Na^+-H^+ exchanger[7] and that protons interact with the erythrocyte Na^+-Li^+ exchanger.[8] On the other hand, Na^+-H^+ exchange is amiloride sensitive,[7] but erythrocyte Na^+-Li^+ exchange is resistant to this agent.[9] Taken together, the data seem to suggest that the renal Na^+-H^+ exchanger and the red cell Na^+-Li^+ countertransport system are not identical but may represent different modes of operation of the same or related transport systems.

The idea that Na^+-H^+ exchange is involved in the pathogenesis of hypertension has been bolstered by several recent observations. First, cultured vascular smooth muscle cells from spontaneously hypertensive rats had significantly higher Na^+-H^+ exchange activity than cells from normotensive Wistar-Kyoto rats.[10] In other work, intact blood vessels from 5-week-old spontaneously hypertensive rats were more alkaline than similar vessels from Wistar-Kyoto rats, possibly due to increased Na^+-H^+ exchange in the former. A study in humans also supports the idea that hypertension is related to increased activity of Na^+-H^+ exchange. Platelets from untreated hypertensive subjects exhibited enhanced swelling on adding sodium propionate when compared with normal controls.[11] This activity is probably due to increased

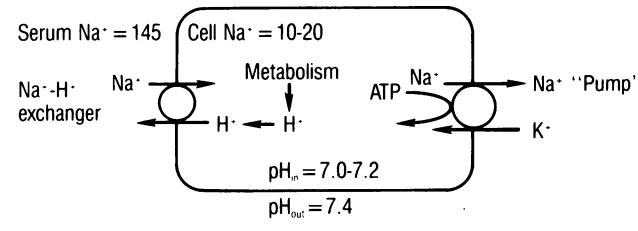

Figure 2.—The sodium-hydrogen ion (Na^+-H^+) exchanger is found in virtually all cells and is responsible for removing acid generated by metabolic processes within the cell. The Na^+-H^+ exchanger uses as its energy source the Na^+ gradient generated by the Na^+ pump. In renal proximal tubule epithelial cells, the Na^+-H^+ exchanger is localized to the tubular lumen, and the Na^+ pump is on the opposite side of the cell, facing the circulation. This disposition of the transport systems enables the cell to effect net transepithelial Na^+ absorption and H^+ secretion. The fact that common ion transporters are used by renal epithelial cells to effect salt transport raises the possibility that agents which regulate salt transport in the kidney might also affect the intracellular ionic milieu in other cells, including vascular smooth muscle cells. ATP = adenosine triphosphate

Na^+-H^+ exchange in the platelets obtained from hypertensive subjects.

Is increased activity of Na^+-H^+ or Na^+-Li^+ exchange causally related to hypertension, or is it an epiphenomenon arising from other alterations in erythrocytes, platelets, and smooth muscle cells from diseased arteries? Before trying to answer this question, we should briefly consider the mechanisms by which Na^+-H^+ exchange activity can be increased. The regulation of the Na^+-H^+ exchanger in vascular smooth muscle is complex and appears to involve allosteric mechanisms, covalent modification, de novo synthesis, and physical alterations of the membrane. The binding constants for Na^+ and H^+ on the exchanger are close to their physiologic concentrations within the cell. Therefore, changes in the cell pH or cell Na^+ will affect exchanger activity allosterically. Numerous growth factors and vasoconstrictors (including angiotensin II, vasopressin, and endothelin) activate the exchanger through second messenger systems. These have not been fully elucidated, but one such messenger appears to be diacylglycerol, acting on protein kinase C. This enzyme presumably phosphorylates the exchanger or a related membrane protein. Certain hormones (thyroid, glucocorticoids) and environmental factors (acidosis, hypokalemia) appear to increase renal epithelial Na^+-H^+ exchange over hours to days, probably by de novo synthesis of the transporter. This phenomenon may also occur in vascular smooth muscle, but this has not been carefully examined. Finally, osmotic agents through cell shrinkage dramatically activate the exchanger in many cell types, including vascular smooth muscle. The point of this brief summary is that increased Na^+-H^+ exchange activity might be a primary defect in hypertension, or, more likely, it might be a secondary phenomenon arising from altered intracellular Na^+ or pH, increased angiotensin II, vasopressin, endothelin, glucocorticoids, or even shape changes in the cells under study. To date, there is no convincing evidence that increased Na^+-H^+ exchange is a primary defect in hypertension.

Canessa and colleagues and other investigators have found that hypertensive subjects and their normotensive relatives exhibited comparably increased erythrocyte Na^+-Li^+ countertransport, suggesting that increased activity may be a predisposing genetic factor but that it does not itself cause increased blood pressure.[6] Several groups have reported lower rates of red cell Na^+-Li^+ countertransport in African Americans compared with whites; furthermore, they find no relationship between transport and blood pressure in African Americans.[12] With regard to Na^+-H^+ exchange, Livne and associates found that patients with treated hypertension had significantly lower rates of platelet Na^+-H^+ exchange than those with untreated hypertension.[11] These findings suggest that differences in the phenotypic expression or activation of the Na^+-H^+ exchange may be associated with hypertension but actually argue against a causal role for increased transport in the disease.

If increased Na^+-H^+ exchange is indeed a primary defect in essential hypertension, the link between its operation and increased vasomotor tone has yet to be made. Increased Na^+-H^+ exchange activity could have several effects on the vascular smooth muscle cell, including increased cell Na^+, increased pH, and increased cell volume. According to the Blaustein hypothesis, increased cell Na^+ would elevate cell Ca^{2+} by action of the Na^+-Ca^{2+} exchange system.[2] Sodium-calcium exchange has a well-established role in Ca^{2+} metabolism in nerve and cardiac muscle where it was originally described. Although Na^+-Ca^{2+} exchange activity has been found by a number of investigators both in intact vascular smooth muscle cells[13] and in plasma membranes from these cells,[14] its physiologic role in vascular smooth muscle has been surprisingly difficult to ascertain.

Sodium-Calcium Exchange

Isolated plasma membrane vesicles have been the preparation of choice for the study of many membrane transport systems. Unfortunately, Na^+-Ca^{2+} exchange activity in smooth muscle membranes appears to be low, at most 1% of that found in cardiac muscle membranes.[14] This may be due to a loss of activity or activating factors in the preparation. Alternatively, Na^+-Ca^{2+} exchange may not be abundant in smooth muscle.

Early studies with intact vascular smooth muscle systems clearly showed that replacing medium Na^+ with other cations significantly increased isotopic Ca^{2+} influx and caused contraction of vascular strips (reviewed by Blaustein[2]). These findings were interpreted to mean that the plasma membrane of vascular smooth muscle cells contains an Na^+-Ca^{2+} exchange system and that Na^+ removal leads to rapid Na^+ efflux and Ca^{2+} entry. The removal of extracellular Na^+, however, is a drastic maneuver with several potential nonspecific effects. These include alterations in surface charge, membrane potential, Ca^{2+} or other ion channel activity, and Na^+ pump activity. Any of these secondary effects could alter the contractile state or Ca^{2+} transport nonspecifically. The interpretation of such experiments is also clouded by the possibility of Na^+-Ca^{2+} exchange at extracellular Ca^{2+} binding sites. More recently, Smith and co-workers have found that the removal of extracellular Na^+ reveals abundant Na^+-Ca^{2+} exchange activity in cultured aortic smooth muscle cells. Such activity is latent, however, unless the cell Na^+ content is raised from the basal value of 7 mmol per liter to approximately 25 mmol per liter.[13] In the platelet, a cell often used as a model for vascular smooth muscle, neither Na^+ removal nor ouabain alter the intracellular Ca^{2+}.[15] Thus, Na^+-Ca^{2+} exchange has been an elusive link in transport theories of hypertension. Further work in this area is essential before we can accept the idea that this transport system plays a central role in the pathogenesis of hypertension.

Sodium-Hydrogen Exchange and Intracellular Calcium: Is There a Link?

Even if we accept the hypothesis that Na^+-Ca^{2+} exchangers play an important role in vascular smooth muscle Ca^{2+} metabolism, it is not clear that physiologic changes in intracellular Na^+ are sufficient to alter cell Ca^{2+} significantly in vascular smooth muscle. Blaustein argued that the Na^+-Ca^{2+} exchange would carry three Na^+ ions and would therefore be highly sensitive to small changes in Na^+ concentration.[2] To test this hypothesis, Mitsuhashi, working in my laboratory, asked whether physiologic alterations in the Na^+-H^+ exchange activity would alter intracellular Ca^{2+} in cultured vascular smooth muscle cells.[16] She used three potent stimuli of Na^+-H^+ exchange. The first was phorbol myristate acetate, which works by activating protein kinase C and which is also known to cause contraction of vascular smooth muscle. The second was osmotically induced cell shrinkage, and the third was cell acidification by ammonium chloride prepulse. Surprisingly, all three stimuli activated the Na^+-H^+ exchange as expected, but none of them had any measurable effect on the intracellular Ca^{2+}.[16] Other investigators, working with different cell types, have shown that in some cases phorbol esters activate the Na^+-H^+ exchanger but actually decrease the cell Ca^{2+} content.[17] If

such potent stimuli of Na^+-H^+ exchange do not increase the cell Ca^{2+} concentration, it is difficult to envisage how small changes in the Na^+-H^+ exchange such as those reported in platelets[11] could be expected to increase the cell Ca^{2+} content.

Calcium and the Mechanism of Contraction of Vascular Smooth Muscle

Most hypotheses linking abnormalities in ion transport to hypertension consider intracellular Ca^{2+} as the final common mediator of vascular tone. It is surprising that this assumption receives relatively little debate because the control of vascular smooth muscle tone appears to be more complex than this. Assumptions about the primacy of Ca^{2+} regulation in vascular smooth muscle derive from well-established information obtained from skeletal and cardiac muscle. In these systems, the myosin ATPase is regulated by the troponin-tropomyosin system. Calcium binds to troponin C, causing a conformational change that is transmitted to the remainder of the troponin complex and to tropomyosin. These conformational changes allow actin to interact with myosin and to activate the myosin ATPase. Myosin-ATPase activity induces movement of the myosin head along the actin strand. Thus, contractile force and cell Ca^{2+} appear to be well correlated in skeletal and cardiac muscle.

Smooth muscle myosin ATPase is not regulated in this way. In smooth muscle, the regulation of contractile activity occurs on the myosin filament itself. One of the components of the myosin head, the myosin light chain, can be reversibly phosphorylated. Myosin light-chain kinase, an exquisitely Ca^{2+}-sensitive enzyme, is one of several enzymes that phosphorylate the myosin light chain. After membrane depolarization or hormonal activation, smooth muscle cell Ca^{2+} rises, the myosin light chain becomes phosphorylated, and a contractile force develops.[18] In tracheal smooth muscle, there is a close relationship between the level of intracellular Ca^{2+} and myosin light-chain phosphate content; moreover, this relationship is invariant for several hormonal agonists and a Ca^{2+} ionophore. In response to a variety of agonists, light-chain phosphate content also correlates well with the initial shortening velocity of vascular smooth muscle strips.[19] Thus, it seems likely that contraction is initiated by a rise in the cell Ca^{2+} content that leads to activation of the myosin light-chain kinase, an increase in light-chain phosphate content, and the development of tension.

Unfortunately, this straightforward model of smooth muscle contraction cannot explain all aspects of the smooth muscle contractile response. Several types of experiments have shown that the relationship between intracellular Ca^{2+} and light-chain phosphate content can be dissociated when the two variables are measured and compared after hormone action versus membrane depolarization. More important, the relationship between intracellular Ca^{2+} and contractile force in vascular smooth muscle is not unique. In rat aortic smooth muscle, norepinephrine caused contraction at considerably lower Ca^{2+} levels than did ionomycin, a Ca^{2+} ionophore.[19] In fact, contraction in response to low concentrations of norepinephrine was found in the absence of demonstrable rises in the cell Ca^{2+} content.[19] As mentioned earlier, the activation of protein kinase C by phorbol esters causes contraction of vascular smooth muscle without raising the cell Ca^{2+} content measurably. Even more surprising is the finding that carbachol (a contractile agonist) and isoproterenol (a smooth muscle relaxant) both raised the Ca^{2+} levels equally in tracheal smooth muscle strips.[20]

The role of Ca^{2+} in determining vascular tone is even less clear when considering the tonically contracted vascular smooth muscle cell. After the initial development of a contractile force, the cell contractile system enters the "latch" state, in which tension is maintained despite a greatly diminished rate of cross-bridge formation and adenosine triphosphate use.[18] Because hypertension is probably due to tonic increases in smooth muscle tone and not to transient increases, this latch state is of great importance in understanding hypertension. Yet, remarkably little is known about how this state of contraction is maintained. What is known is that during maintained contraction, cell Ca^{2+} and myosin light-chain phosphorylation levels actually fall to basal or near-basal levels. Recent evidence in molluscan smooth muscle shows that the "catch" state, analogous to the latch state in mammalian smooth muscle, is maintained with cell Ca^{2+} at its basal level.[21] Moreover, relaxation of the catch state involves no change in cell Ca^{2+} concentration. Thus, latch states appear to be maintained by increasing the sensitivity of the contractile machinery to Ca^{2+} or, alternatively, by a Ca^{2+}-independent mechanism. Much more needs to be learned about the maintenance of these smooth muscle latch states before we can understand the maintenance of vascular tone.

In summary, Ca^{2+} is probably not the sole actor in the contraction of vascular smooth muscle cells. At the least, some agents, like norepinephrine, appear to increase the cell Ca^{2+} concentration and to also increase the sensitivity of the contractile mechanism to Ca^{2+}. The data do not have to be stretched far to suggest that Ca^{2+}-independent modes of contraction may also exist. Thus, models of hypertension are not forced to include increased cell Ca^{2+} content as the basis for the defect. Rather, in some persons, hypertension may be due to an altered sensitivity of the vascular contractile system to Ca^{2+} or even to Ca^{2+}-independent processes.

Some Possible Future Directions

Where should we now turn in the quest for a pathophysiologic basis for essential hypertension? Abnormalities in ion transport, as discussed, may yet hold the key to understanding the disease, but the missing links in this theory are still significant. Rather than discussing all other potential avenues for research in essential hypertension, I will limit my discussion to three areas that appear to hold promise for the future. The first is the existence of local renin-angiotensin systems in the vasculature and other tissues, the second is control of vascular tone by the endothelium, and the last is the role of smooth muscle cell hypertrophy in hypertension.

Local Renin-Angiotensin Systems

The role of the circulating renin-angiotensin system in the control of blood pressure has long been appreciated. More recent evidence indicates that the components of the renin-angiotensin system are produced locally in several tissues other than the kidney. Renin or angiotensin produced by these local systems may influence the blood pressure without ever reaching the circulation.

As long ago as the 1960s, there were indications that some renin is found in isolated blood vessels. While it is still not clear how much of this renin is produced locally and how much is trapped from the circulation, there is evidence that renin is produced in vascular smooth muscle cells,[22] and other evidence suggests that angiotensinogen and angiotensin-converting enzyme are also present in the vessel

wall. These data led to the hypothesis that angiotensin II produced within the vessel wall plays an important role in the control of blood pressure.[23] The existence of this system may explain why many hypertensive persons with normal or low levels of circulating renin respond well to converting-enzyme blockade.[24]

The renin-angiotensin system has also been found in other tissues, including the adrenal gland, brain, and placenta. A recent experiment using transgenic rats provides further support for the notion that locally produced renin and angiotensin may play a role in hypertension. Transfer of the mouse *ren-2* renin gene to rats caused severe hypertension in virtually all offspring expressing the gene product.[25] The hypertension was at least partially correctable with converting enzyme inhibitors. Surprisingly, circulating renin, angiotensin I, and angiotensin II were all suppressed in these animals. Of the tissues examined, the adrenal gland showed the highest levels of expression of the transgene. Thus, the adrenal gland may be another site where the renin-angiotensin system can influence the blood pressure without entering the circulation.

The Endothelium and Vascular Tone

Newly discovered vasoactive substances produced by the endothelial cell may also play a crucial role in the development of hypertension.[26] These substances may act directly on adjacent smooth muscle cells and affect vasomotor tone without entering the circulation. An excellent example of this phenomenon is the endothelium-derived relaxing factor, discovered by Furchgott and Zawadzi in 1980.[27] This agent, whose chemical identity is probably nitric oxide,[28] is released from endothelial cells in response to a variety of hormonal and physical factors. Because the half-life of nitric oxide is so short (several seconds), it probably acts to relax only the subjacent vascular smooth muscle cells before becoming rapidly inactivated in the circulation. Although the precise role for endothelium-derived relaxing factor in either normal or disordered cardiovascular function is still not clear, its mechanism of action is of therapeutic importance because the nitrate vasodilators appear to act by the same cellular mechanism as endothelium-derived relaxing factor.

A potent endothelium-derived vasoconstrictor, endothelin, has also recently been discovered.[29] This 21-amino acid peptide, a close relative of the asp venom toxin, sarafotoxin 6B, is released from cultured mammalian endothelial cells by thrombin, increased intracellular Ca^{2+}, and possibly by physical forces acting on the cell surface. Like endothelium-derived relaxing factor, endothelin does not appear to circulate significantly, but rather may act directly on the subjacent vascular smooth muscle cell to cause contraction.

Hypertrophy and Hyperplasia of Vascular Smooth Muscle Cells

Arteries and arterioles from persons with hypertension have long been known to contain an increased mass of vascular smooth muscle cells. In some vessels, this is due to hypertrophy of existing smooth muscle cells, while in others it is due to an increased number of cells (hyperplasia).[30] Whether it be associated with hypertrophy or hyperplasia, increased DNA synthesis in vascular smooth muscle cells is a prominent early feature of all forms of hypertension (Figure 3).[31] Although hypertrophy of blood vessels is often thought to be a cellular response to elevated pressures, there is considerable evidence that DNA synthesis can occur before the increase in pressure in some experimental models. For example, Carlier and associates found that DNA synthesis peaked at four days after one-kidney, one-clip hypertension was induced, long before the maximal blood pressure is reached.[32] Over the next two to three weeks, DNA synthesis fell towards control levels. Loeb and colleagues also found that DNA synthesis preceded the onset of hypertension in the two-kidney, one-clip model.[33] Thus, cell proliferation may play a crucial role in maintaining hypertension that is established by a wide range of causes.

What is the stimulus to hypertrophy or hyperplasia of vascular smooth muscle cells in hypertension? While this question has still not been answered, several possibilities have clearly emerged as the result of recent research on the biology of platelets, endothelial cells, and vascular smooth muscle cells themselves. These possibilities include a direct effect of wall stretch on cell growth, circulating mitogenic factors, the release of mitogenic factors by endothelial cells or platelets, and autocrine or paracrine regulation of growth by the smooth muscle cell itself.

Increased wall tension appears to play a role in the development of vascular hypertrophy in hypertension. In several experimental models, it has been found that a reduction of the blood pressure by various means will reduce or reverse the vascular hypertrophy. Stretch has been found to greatly enhance the production of a variety of extracellular matrix components in vascular smooth muscle.[34] Regional blood flow may also be a determinant of vascular wall thickness. Thus, physical factors that normally play a role in the modeling of vessel thickness may cause pathologic changes when the blood pressure becomes abnormally high.

Humoral factors involved in the development of hypertension could also exert a direct influence on the growth of vascular smooth muscle cells. In general, it has been difficult to separate the direct effects of humoral factors from those caused by hypertension itself. There is some evidence for a role of renin and angiotensin in vascular hypertrophy. Plunkett and Overbeck found that in coarctation hypertension, vascular hypertrophy was demonstrable in a normotensive bed below the level of the coarctation,[35] but there is as yet no general agreement on this point. Angiotensin does exhibit growth factor activity against cultured vascular smooth muscle cells, but it is probably not a potent mitogen. On balance, the role of renin and angiotensin in the development of vascular hypertrophy is probably limited.

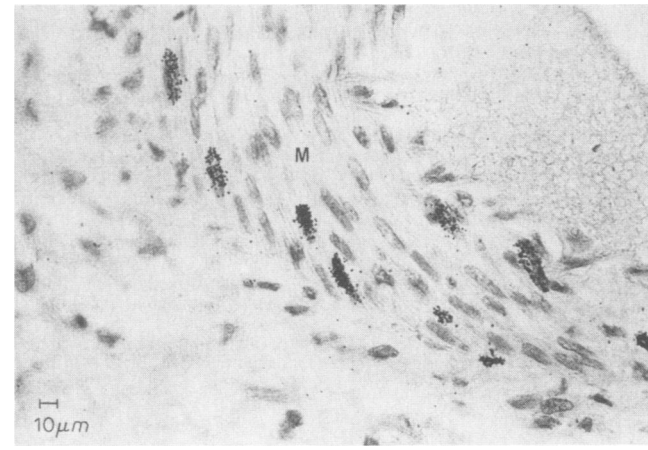

Figure 3.—The distribution of ^{3}H-thymidine is shown in medial smooth muscle cells of a small muscular artery from a rabbit with hypertension induced by coarctation of the aorta. DNA synthesis is demonstrated in smooth muscle cells throughout the thickness of the media. After autoradiography, slides were stained with hematoxylin and eosin (from Bevan[31]).

Other circulating factors could also play a role in the development of vascular hypertrophy. Catecholamines stimulate the proliferation of vascular smooth muscle cells,[36] and innervation by sympathetic nerves appears to be an important trophic factor in blood vessels. Serotonin is also a potent mitogen in vascular smooth muscle cells.[37] Thus, any of various circulating factors could play a role in the development of vascular hypertrophy.

New information suggests that local factors in the vascular wall play perhaps an even more important role than humoral factors in the control of smooth muscle cell proliferation. Local damage to the endothelial cell layer can lead to the activation of platelets with the release of platelet-derived growth factor, epidermal growth factor, serotonin, and transforming growth factor-β, all of which have mitogenic activity. Prostaglandins and thromboxanes may also play a role in the proliferative response. Endothelial cells themselves can be stimulated to release mitogenic factors, including the B chain of platelet-derived growth factor, fibroblast growth factor, and endothelin. Both platelet activation and endothelial damage are prominent early features of hypertensive damage to the vascular wall. Thus, factors produced by these highly reactive cells are likely to play a role in the pathogenesis of vascular hypertrophy.

Last, the vascular smooth muscle cell may respond abnormally in the hypertensive state. The smooth muscle cell is capable of producing growth-promoting (platelet-derived growth factor, insulin-like growth factor I, and interleukin 1) and -inhibiting (heparin) substances. Thus far, little is known about what regulates the synthesis of these substances in vivo. An abnormal in vitro proliferation of smooth muscle cells from spontaneously hypertensive rats is well documented, however.[38] In part, this increased proliferation may be due to a hyperresponsiveness to growth factors. Thus, there is the possibility that hypertension could be induced or maintained by a primary smooth muscle abnormality.

The foregoing discussion is neither an all-inclusive critique of the existing theories of the pathogenesis of hypertension nor a clairvoyant vision of future research in the field. I have tried to show that substantial arguments can be built against some of the existing major theories for the pathogenesis of hypertension and that an infusion of new thinking is needed. Only time and more hard work will reveal the answers in this exciting field.

REFERENCES

1. Haddy FJ, Overbeck HW: The role of humoral agents in volume expanded hypertension. Life Sci 1976; 19:935-948

2. Blaustein MP: Sodium ions, calcium ions, blood pressure regulation, and hypertension: A reassessment and a hypothesis. Am J Physiol 1977; 232:C165-C173

3. Dahl LK, Knudsen KD, Heine M, et al: Effects of chronic excess salt ingestion—Genetic influence on the development of salt hypertension in parabiotic rats: Evidence for a humoral factor. J Exp Med 1967; 126:687-699

4. Hamlyn JM, Harris DW, Ludens JH: Digitalis-like activity in human plasma. J Biol Chem 1989; 264:7395-7404

5. Kelly RA, Smith TW: The search for the endogenous digitalis: An alternative hypothesis. Am J Physiol 1989; 256:C937-C950

6. Canessa M, Adragna N, Solomon HS, et al: Increased sodium-lithium countertransport in red cells of patients with essential hypertension. N Engl J Med 1980; 302:772-776

7. Ives HE, Yee VJ, Warnock DG: Mixed-type inhibition of the renal Na^+/H^+ antiporter by Li^+ and amiloride: Evidence for a modifier site. J Biol Chem 1983; 258:9710-9716

8. Fundus J, Wieth JO, Jensen HE, et al: The sodium/lithium exchange mechanism in essential hypertension—Is it a sodium/proton exchanger?, *In* Villarreal H, Sambhi MP (Eds): Topics in Pathophysiology of Hypertension. The Hague, The Netherlands, Martinus Nijhoff, 1984, pp 147-161

9. Kahn AM: Difference between human red blood cell Na^+-Li^+ countertransport and renal Na^+-H^+ exchange. Hypertension 1987; 9:7-12

10. Berk BC, Vallega G, Muslin AJ, et al: Spontaneously hypertensive rat vascular smooth muscle cells in culture exhibit increased growth and Na^+/H^+ exchange. J Clin Invest 1989; 83:822-829

11. Livne A, Veitch R, Grinstein S, et al: Increased platelet Na^+-H^+ exchange rates in essential hypertension: Application of a novel test. Lancet 1987; 1:533-536

12. Weder AB, Toretti BA, Julius S: Racial differences in erythrocyte cation transport. Hypertension 1984; 6:115-123

13. Smith JB, Zheng T, Smith L: Relationship between cytosolic free Ca^{2+} and Na^+-Ca^{2+} exchange in aortic muscle cells. Am J Physiol 1989; 256:C147-C154

14. Grover AK, Kwan CY, Rangachari PK, et al: Na-Ca exchange in a smooth muscle plasma membrane-enriched fraction. Am J Physiol 1983; 244:C156-C165

15. Brass LF: The effect of Na^+ on Ca^{2+} homeostasis in unstimulated platelets. J Biol Chem 1984; 259:12571-12575

16. Mitsuhashi T, Ives HE: Intracellular Ca^{2+} requirement for activation of the Na^+-H^+ exchange in vascular smooth muscle cells. J Biol Chem 1988; 263:8790-8795

17. Moolenar WH, Tertoolen LG, deLaat SW: Phorbol ester and diacyglycerol mimic growth factors in raising cytoplasmic pH. Nature 1984; 312:371-374

18. Kamm KE, Stull JT: The function of myosin and myosin light chain kinase phosphorylation in smooth muscle. Annu Rev Pharmacol Toxicol 1985; 25:593-620

19. Bruschi G, Bruschi ME, Regolisti G, et al: Myoplasmic Ca^{2+}-force relationship studied with fura-2 during stimulation of rat aortic smooth muscle. Am J Physiol 1988; 254:H840-H854

20. Takuwa Y, Takuwa N, Rasmussen H: The effects of isoproterenol on intracellular calcium concentration. J Biol Chem 1988; 263:762-768

21. Ishi N, Simpson AWM, Ashley CC: Free calcium at rest during 'catch' in single smooth muscle cells. Science 1989; 243:1367-1368

22. Re R, Fallon JT, Dzau V, et al: Renin synthesis by canine aortic smooth muscle cells in culture. Life Sci 1982; 30:99-106

23. Dzau VJ: Significance of the vascular renin-angiotensin pathway. Hypertension 1986; 8:553-559

24. Waeber B, Gavras I, Brunner HR, et al: Prediction of sustained antihypertensive efficacy of chronic therapy with captopril: Relationships to immediate blood pressure response and control plasma renin activity. Am Heart J 1982; 103:384-390

25. Mullins JJ, Peters J, Ganten D: Fulminant hypertension in transgenic rats harbouring the mouse *Ren-2* gene. Nature 1990; 344:541-544

26. Daniel TO, Ives HE: Endothelial control of vascular function. News Physiol Sci 1989; 4:139-142

27. Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980; 288:373-376

28. Palmer RMJ, Ferrige AG, Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987; 327:524-526

29. Yanagisawa M, Kurihara H, Kimura S, et al: A novel potent vasoconstrictor produced by vascular endothelial cells. Nature 1988; 332:411-415

30. Owens GK, Rabinovitch PS, Schwartz SM: Smooth muscle cell hypertrophy versus hyperplasia in hypertension. Proc Natl Acad Sci USA 1981; 78:7759-7763

31. Bevan RD: An autoradiographic and pathologic study for cellular proliferation in rabbit arteries correlated with an increase in arterial pressure. Blood Vessels 1976; 13:100-128

32. Carlier PG, Rorive G, Barbason H: Kinetics of proliferation of rat aortic smooth muscle cells in Goldblatt one-kidney, one-clip hypertension. Clin Sci 1983; 65:351-357

33. Loeb AL, Mandel HG, Straw JA, et al: Increased aortic DNA synthesis precedes renal hypertension in rats—An obligatory step? Hypertension 1986; 8:754-761

34. Leung DYM, Glagov S, Matthews MB: Cyclic stretching stimulates synthesis of matrix components by arterial smooth muscle cells in vitro. Science 1976; 191:475-477

35. Plunkett WC, Overbeck HW: Increased arteriolar wall-to-lumen ratio in a normotensive vascular bed in coarctation hypertension. Am J Physiol 1985; 249:H859-H866

36. Blaes N, Boissel JP: Growth-stimulating effect of catecholamines on rat aortic smooth muscle cells in culture. J Cell Physiol 1983; 116:167-172

37. Kavanaugh WM, Williams LT, Ives HE, et al: Serotonin-induced deoxyribonucleic acid synthesis in vascular smooth muscle cells involves a novel, pertussis toxin-sensitive pathway. Mol Endocrinol 1988; 2:599-605

38. Scott-Burden T, Resink TJ, Baur U, et al: Epidermal growth factor responsiveness in smooth muscle cells from hypertensive and normotensive rats. Hypertension 1989; 13:295-304